Gene Environment Interactions and Behavior

Exposure to **psychosocial stressors** during vulnerable periods of **pregnancy** and **early childhood** can interact with genotype to **permanently alter gene expression** causing adverse **neurobehavioral** outcomes.

General Information	
Broad Focus Area	Neurodevelopment and Behavior
Background and Justification	According to the Global Burden of Disease Study, depression is ranked as the fourth most important cause of death and disability.[1,2] Not only is it a major cause of suicide and lost productivity, it is also associated with a worse prognosis for coronary heart disease patients, and predicts mortality in previously healthy individuals.[3-11] The worst outcome of depression is suicide, which accounts for 6.8% of all deaths in 10-14 year olds and 11.9% of deaths in 15-19 year olds.[12] Physical violence is also a serious problem in adolescents. In 2003, 17% of American high school students carried a weapon (gun, knife or club) and 33% were involved in physical fights [13]. Depression and violent behaviors are psychosocial problems illustrative of many such outcomes that present the opportunity to examine the interaction of genetic susceptibility and a range of social and other exposures. Despite its obvious public health significance, efforts to find a cure for depression have been confounded by lack of a clear understanding of its complex etiology, and similar obstacles have confronted attempts to curb youth violence and aggression. One reason for the inconsistency seems to be the influence of the environment on gene expression. The National Children's Study provides an opportunity for the examination of gene/environment interactions that is unparalleled in history and should be utilized to the fullest. Gene expression is subject to multiple environmental influences: social connections, material resources (e.g., nutrition), and toxic exposures. A large cohort is needed to provide enough power for the candidate gene approach to study these neurobehavioral outcomes, while accounting for multiple interactions. Research on non-human primates has demonstrated the influence of mothering on gene expression. These data further illustrate that knowing the genotype is not sufficient for predicting phenotypic expression without additional knowledge of the psychosocial environment.[14] Intra- and extracellular environments play an important role not only in the magnitude of expression but in the direction of expression, i.e., whether it is up- or down-regulated. The intracellular environment is a function not only of its genetic components, but of influences from the extracellular factors such as hormones, neurotransmitters, cytokines, and nutrients.[15] Variation in these constituents can determine how and when a gene is functionally expressed. Psychosocial factors are involved in these interactions through their influence on hormones and neurotransmitters. Understanding function requires knowledge of the factors that influence when and in what direction (e.g., up or down regulation) it is expressed.
Prevalence/ Incidence	Major depressive disorder affects up to 2.5% of children and 8.3% of adolescents, an age group where the female-to-male ratio of depression is 2:1.[16] The frequency of the "l" form of the serotonin transporter gene is about 60% (50-60% in Caucasians and close to 70% in African Americans). Therefore the gene frequency is .36 for the "ll" variant, .48 for the "ls" variant and .16 for the "ss"

	variant. An estimated 3%-8% of children born in the U.S. each year have neurobehavioral problems.[17]
Economic Impact	The annual cost of depression in the United States ranges between $43.7 billion and $52.9 billion in 1990. Adjusted for inflation, this estimate would be close to $70 billion today.[18] While no studies have precisely calculated all of the costs associated with autism, a U.K. report estimates the lifetime custodial costs of autism spectrum disorders in the range of $3-$4 million per child, with societal costs likely to be triple the individual estimate.[19, 20] The lifetime costs of mental retardation for persons born in 2000 were estimated at $51.2 billion (in 2003 dollars).[21]

Exposure Measures		**Outcome Measures**	
Primary/ Maternal	Exposure to psychosocial stressors during pregnancy	***Primary/ Maternal***	
Methods	Questionnaire; Clinical diagnosis	Methods	
Life Stage	Pregnancy	Life Stage	
Primary/ Child	Genotype - 5-HTTLPR genotype; MAOA genotype Psychosocial environment - stress hormones/cortisol; qualitative environmental assessments	***Primary/ Child***	Depression; antisocial behavior, other psychosocial and neurobehavioral outcomes
Methods	- Blood for genotyping - Salivary cortisol at 6 months, 1 year, 2 years, 3 years - Parenting style: nurturance, discipline techniques - Measure of depression in parents - Measure(s) of child abuse: parental discipline style, records from child protective services	Methods	Measures of depression Measurement of adolescent antisocial behavior (DSM-IV criteria for adolescent) - Conduct disorder - Convictions for violent crimes - Medical records review - School record review - Observations of family/friends
Life Stage	First 3 years and beyond	Life Stage	Childhood, adolescence

Important Confounders/Covariates	
Smoking	Nicotine induced c-fos mRNA expression was found in several brain areas associated with cognitive function in rats. This may be associated with development of schizophrenia in adults.[22]
Mental health during pregnancy	High prenatal stress and low social support may have influence on fetal development and birth outcomes.[23]
Parental depression	Parental depression may influence child depression and other behavior

Population of Interest	**Estimated Effect that is Detectable**
All Children	Power for the environmental interactions with the serotonin transporter gene was calculated with three variants of the allele, three levels of stress, .05 probability and 80% power. The frequency of the “l” form of the

		serotonin transporter gene is about 60% (50-60% in Caucasians and close to 70% in African Americans). Therefore the gene frequency is .36 for the "ll" variant, .48 for the "ls" variant and .16 for the "ss" variant. To achieve 80% power, the total number of people required is 47,920. Genes for MAOA are located on the X chromosome. The two most common variable number tandem repeat (VNTR) polymorphisms account for about 96% of the population (21, supplemental material). They contain 3 repeats (low activity) and 4 repeats (high activity), respectively. They are present in about 33% and 62% respectively. Child abuse in the study cited was 8% severe, 28% probable abuse and 64% with no abuse. Power analyses based on a prevalence of 5% in the unexposed population (conservative according to Caspi's results) result in a required sample size of 31,650.

Other Design Issues	
Ethical/Burden Considerations	Human subjects issues associated with observation of certain psychosocial stressors (e.g. abuse) must be carefully addressed in the study protocol, with any planned remedial actions approved by appropriate institutional review board (IRB).
Cost/Complexity of Data Collection	The longitudinal design is required because it is important to trace the development of the cohort through childhood and adolescence, in order to measure not only the exposures, but the neurobehavioral outcomes of relevance (e.g., depression, substance abuse, antisocial behavior). Several reports from smaller cohorts have indicated childhood antecedents (or perhaps risk factors) that can predate symptom development by long periods.

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